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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,681	02/20/2007	Sergei Anatolievich Lukyanov	U 015745-9	6233

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,681	LUKYANOV ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04/30/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-8,13,17,28 and 30-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-8,13,17,28 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/30/2010 has been entered.

Claims 2-4, 12, 18-27, and 29 are cancelled. Claims 1, 13, and 30-32 are amended.

Claims 1, 5-11, 13-17, 28, and 30-33 are pending.

Claims 9-11 and 14-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 5-8, 13, 17, 28, and 30-33 are currently under examination to the extent of elected SEQ ID NO: 9 (705 nucleotides) that encodes the elected SEQ ID No. 10 (234 amino acid residues).

This application 10/532,681 is a 371 of PCT/RU03/00474 filed on 11/05/2003 which claims benefit of 60/425,570 filed on 11/12/2002, and claims benefit of 60/429,795 filed on 11/27/2002, and claims benefit of 60/464,258 filed on 04/21/2003, and claims benefit of 60/480,080 filed on 06/20/2003.

Priority

The following statements were documented in the Final office action mailed on 01/08/2010. The statements are updated to reflect the status of claims field on 04/07/2010.

It is noted that provisional applications 60/429,795 filed on 11/27/2002, 60/464,258 filed on 04/21/2003, and 60/480,080 filed on 06/20/2003, did not disclose either SEQ ID No: 10 or SEQ ID No: 9. The provisional application 60/425,570 filed on 11/12/2002 discloses SEQ ID No 2 that is identical to the SEQ ID No: 10 of instant application, but 60/425,570 filed on 11/12/2002 did not disclose SEQ ID No.9 of instant application since SEQ ID No. 1 and SEQ ID No. 3 disclosed in 60/425,570 are not the same as SEQ IN No. 9 of instant application

Therefore, the priority date of claim 1, which recites SEQ ID No. 10 and its dependent claims 5-8, 13, 17, 27, 28, 31, and 33 is determined to be 11/12/2002, the filing date of provisional application 60/425,570. The priority date of claims 30 and 32, which recites SEQ ID No. 9, is determined to be 11/05/2003, the filing date of PCT/RU03/00474.

In the reply filed on 05/14/2009, Applicant argues that claim 30 should be entitled to the priority date of 11/12/2002. However, Applicant fails to specifically point to the disclosure of SEQ ID No: 9 in the provisional application 60/425,570, filed on 11/12/2002. The priority date of claims 30 and 32, which recites SEQ ID No. 9, remains to be 11/05/2003, the filing date of PCT/RU03/00474.

Applicant's remarks filed on 04/07/2010 did not provide any further arguments in this regard.

Sequence compliance

Applicant filed sequence listing on 04/07/2010 and as of 04/20/2010 the USPTO PALM record of Biotech Information indicates "CRF IS GOOD TECHNICALLY / ENTERED INTO DATABASE" for instant application.

Claim Objections

1. Claim 30-33 are objected to because of the following informalities: **(i)** The limitation "Claim 1" recited in claims 31-33 should read as "claim 1" unless capital C is meant to convey a specific meaning. **(ii)** To improve the clarity of claims 30 and 32, the phrase "having a nucleotide sequence ---" recited in claims 30 and 32 should be replaced by a wherein clause. Appropriate correction is required.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Previous rejection of claims 1, 5-8, 13, 17, 28, and 30-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended.

Amended claim 1 filed on 04/07/2010 reads as follows: An isolated nucleic acid molecule encoding a fluorescent protein, wherein said protein has at least 90% identity with full length SEQ ID NO: 10.

Amended claim 13 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to claim 1, wherein said nucleic acid comprises a sequence that is identical to a nucleotide sequence of at least 300 contiguous nucleotides in length of SEQ ID NO: 9.

Amended claim 28 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to the claim 1 which encodes full length SEQ ID NO: 10.

Amended claim 30 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to claim 1, having a nucleotide sequence comprising full length SEQ ID NO: 9.

Amended claim 31 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to Claim 1, wherein said nucleic acid molecule encodes a fluorescent protein having at least 95% identity with full length SEQ ID NO: 10.

Amended claim 32 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to Claim 1, having a nucleotide sequence having at least 95% identity with full length SEQ ID NO:9.

With regard to claim 33, Applicants states that claim 33 is included in the pending claims for its recitation of the structural element that provides for the fluorescence activity of the protein of claim 1. Applicant states that it is the Applicants' position that the presence of a fluorophore is, in fact, implied in claim 1 by the requirement that the nucleic acid of claim 1 encode a protein that is fluorescent. Nonetheless, Applicants have provided claim 33 to recite this structural element, should the recitation of 90% identity to SEQ ID NO: 10 be deemed an insufficient structural description by the Office.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Previous written description rejection of claims 1, 5-8, 13, 17, 28, and 30-33 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is ***withdrawn*** because Applicant's arguments in combination with claim amendments filed on 04/07/2010 have been fully considered and found persuasive.

Applicant argues that the specification teaches 7 examples of nucleic acids that encode proteins with at least 90% identity to full length SEQ ID NO: 10. These include wild type

phiYFP (SEQ ID NO: l, encoding SEQ ID NO: 2) and phiYFP mutants Y1 (SEQ ID NO:3, encoding SEQ ID NO:4), M0 (SEQ ID NO:5, encoding SEQ ID NO:6), M1 (SEQ ID NO:7, encoding SEQ ID NO: 8), M1 humanized (SEQ ID NO:9, encoding SEQ ID NO: 10), M1G1 (SEQ ID NO:17, encoding SEQ ID NO:18), and M1C1 (SEQ ID NO:19, encoding SEQ ID NO:20) (p. 25, I. 5 - p. 27, I. 10). Applicant argues that, thus, the specification provides a description of a number of nucleic acid molecules that encode a fluorescent protein with at least 90% identity to SEQ ID NO: 10 by actual reduction to practice (See pages 8-9 of Applicant's remarks filed on 04/07/2010).

The Examiner agrees that the specification reasonably conveys to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed isolated nucleic acid molecule encoding a yellow fluorescent protein, wherein said yellow protein has at least 90% identity with full length SEQ ID NO: 10. It is emphasized that the written description is directed to "possession" of the claimed isolated nucleic acid molecule. More discussions are provided in the scope of enablement rejection pertaining to the limitation "fluorescent protein" recited in claim 1.

4. Previous scope of enablement claims 1, 5-8, 13, 17, 28, and 30-33 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising of SEQ ID No. 9 that encodes a fluorescent protein consisting of SEQ ID No. 10, and a vector/cell/kit comprising SEQ ID No. 9 that encodes a fluorescent protein consisting of SEQ ID No. 10, does not reasonably provide enablement for (1) any isolated nucleic acid molecule encodes a fluorescent protein other than SEQ ID No. 9 that encodes a fluorescent protein consisting of SEQ ID No. 10, or (2) any vector/cell/kit comprising any

isolated nucleic acid molecule encodes a fluorescent protein other than SEQ ID No. 9 that encodes a fluorescent protein consisting of SEQ ID No. 10, is ***withdrawn*** because the claims have been amended.

Upon further consideration, the following new scope of enablement is necessitated by claim amendments field on 04/07/2010.

5. Claims 1, 5-8, 13, 17, 28, and 30-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule encoding a yellow fluorescent protein, wherein said protein has at least 96% identity with full length SEQ ID NO: 10, and a vector/cell/kit comprising an isolated nucleic acid molecule encoding a yellow fluorescent protein, wherein said protein has at least 96% identity with full length SEQ ID NO: 10, **does not** reasonably provide enablement for (1) said isolated nucleic acid molecule encodes any fluorescent protein other than a yellow fluorescent protein, wherein said protein has at least 96% identity with full length SEQ ID NO: 10, or (2) any vector/cell/kit comprising said isolated nucleic acid molecule encodes any fluorescent protein other than a yellow fluorescent protein, wherein said protein has at least 96% identity with full length SEQ ID NO: 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The nature of the instant invention is drawn to an isolated nucleic acid molecule comprising nucleotide sequences.

Claim 1 amended on 05/14/2009 is directed to an isolated nucleic acid molecule encoding a fluorescent protein, wherein said protein has at least 90% identity with full length SEQ ID NO: 10. Claims 5 and 6 are directed to a vector and an expression vector comprising the nucleic acid of claim 1; Claims 7 and 8 are directed to a cell comprising the nucleic acid of claim 1; Claim 13 is directed to the nucleic acid molecule according to claim 1, wherein said nucleic acid comprises a sequence that is identical to a nucleotide sequence of at least 300 contiguous nucleotides in length of SEQ ID NO: 9. Claim 17 is directed to a kit comprising at least one nucleic acid molecule according to claim 1. Claim 28 is directed to the nucleic acid molecule according to the claim 1 which encodes full length SEQ ID NO: 10. Claim 30 is directed to the nucleic acid molecule according to claim 1, having a nucleotide sequence comprising full length SEQ ID NO: 9. Claim 31 is directed to the nucleic acid molecule according to claim 1, wherein said nucleic

acid molecule encodes a fluorescent protein having at least 95% identity with full length SEQ ID NO: 10. Claim 32 is directed to the nucleic acid molecule according to Claim 1, having a nucleotide sequence having at least 95% identity with full length SEQ ID NO: 9. Claim 33 is directed to the nucleic acid molecule according to Claim 1, wherein the protein comprises a fluorophore.

The specification discloses SEQ ID No. 10, a 234-amino acid long polypeptide, is a humanized version of the phiYFG-M1, which is a mutant form of phiYFP generated by random mutagenesis of phiYFP (an YFP isolated from microorganism *Philalidium* sp.). The specification discloses that SEQ ID No. 9 (a 705-nucleotide long polynucleotide) encodes SEQ ID No. 10. The specification discloses the alignment between GFP (from jelly fish), phiYFP, hydriGFP, and hm2CP in Figure 1. The phiYFP shares only about 50% identities with well characterized GFP (from jelly fish) (See Figure 1 disclosed in specification as well as alignments provided in this office action under 102 rejections).

Based on sequence search performed by the Examiner, it is noted that SEQ ID No. 10 (phiYFG-M1) shares 96% identity with phiYFP (an YFP isolated from microorganism *Philalidium* sp.), Based on sequence search performed by the Examiner, it is noted that SEQ ID No. 10 (phiYFG-M1) shares 96% identity with phiYFP (an YFP isolated from microorganism *Philalidium* sp.), see alignment below.

```
RESULT 1
Q6RYS7_9CNID
ID   Q6RYS7_9CNID            Unreviewed;       234 AA.
AC   Q6RYS7;
DT   05-JUL-2004, integrated into UniProtKB/TrEMBL.
DT   05-JUL-2004, sequence version 1.
DT   24-JUL-2007, entry version 13.
DE   Yellow fluorescent protein.
OS   Phialidium sp. SL-2003.
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OC   Eukaryota; Metazoa; Cnidaria; Hydrozoa; Hydroida; Leptomedusae;
OC   Campanulariidae; Phialidium.
OX   NCBI_TaxID=258839;
RN   [1]
RP   NUCLEOTIDE SEQUENCE.
RX   PubMed=14963095; DOI=10.1093/molbev/msh079;
RA   Shagin D.A., Barsova E.V., Yanushevich Y.G., Fradkov A.F.,
RA   Lukyanov K.A., Labas Y.A., Semenova T.N., Ugalde J.A., Meyers A.,
RA   Nunez J.M., Widder E.A., Lukyanov S.A., Matz M.V.;
RT   "GFP-like proteins as ubiquitous metazoan superfamily: evolution of
RT   functional features and structural complexity.";
RL   Mol. Biol. Evol. 21:841-850(2004).
CC   -----------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   -----------------------------------------------------------------------
DR   EMBL; AY485333; AAR85349.1; -; mRNA.
DR   HSSP; P42212; 1B9C.
DR   GO; GO:0008218; P:bioluminescence; IEA:InterPro.
DR   GO; GO:0006091; P:generation of precursor metabolites and energy; IEA:InterPro.
DR   GO; GO:0018298; P:protein-chromophore linkage; IEA:InterPro.
DR   InterPro; IPR011584; GFP_related.
DR   InterPro; IPR000786; Green_fl_protein.
DR   Pfam; PF01353; GFP; 1.
DR   PRINTS; PR01229; GFLUORESCENT.
DR   ProDom; PD013756; Green_fl_protein; 1.
PE   2: Evidence at transcript level;
SQ   SEQUENCE   234 AA;  26051 MW;  0E7F2DEAAE735D9A CRC64;

  Query Match             96.0%;  Score 1231;  DB 2;  Length 234;
  Best Local Similarity   96.6%;  Pred. No. 1.2e-102;
  Matches  226;  Conservative    3;  Mismatches    5;  Indels    0;  Gaps    0;

Qy          1 MSSGALLFHGKIPYVVEMEGNVDGHTFSIRGKGYGDASVGKVDAQFICTTGDVPVPWSTL 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MSSGALLFHGKIPYVVEMEGNVDGHTFSIRGKGYGDASVGKVDAQFICTTGDVPVPWSTL 60

Qy         61 VTTLTYGAQCFAKYGPELKDFYKSCMPDGYVQERTITFEGDGNFKTRAEVTFENGSVYNR 120
              ||||||||||||||||||||||||||:|||||||||||||| ||||||||||||||||
Db         61 VTTLTYGAQCFAKYGPELKDFYKSCMPEGYVQERTITFEGDGVFKTRAEVTFENGSVYNR 120

Qy        121 VKLNGQGFKKDGHVLGKNLEFNFTPHCLYIWGDQANHGLKSAFKICHEITGSKGDFIVAD 180
              |||||||||||||||||||||||||||||||||||||||||||| ||||||| ||||||
Db        121 VKLNGQGFKKDGHVLGKNLEFNFTPHCLYIWGDQANHGLKSAFKIMHEITGSKEDFIVAD 180

Qy        181 HTQMNTPIGGGPVHVPEYHHMSYHVKLSKDVTDHRDNMSLKETVRAVDCRKTYL 234
              ||||||||||||||||||::||| |||||||||||||| ||||||||||||
Db        181 HTQMNTPIGGGPVHVPEYHHITYHVTLSKDVTDHRDNMSLVETVRAVDCRKTYL 234
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Sinces the phiYFP shares only about 50% identity with well-characterized GFP (from jelly fish), the specification does not provide any enabling support regarding the claimed nucleic acid can encode any fluorescent protein other than a yellow fluorescent protein which has at least 96% identity with full length SEQ ID NO: 10. It is noted that various species of nucleic acid

molecules disclosed in the specification and encompassed by the claimed nucleic acid molecules recited in claim 1 are derived from phiYFP (SEQ ID NO: 2 encoded by SEQ ID NO: l) bearing various point mutations. These nucleic acid molecules include wild type phiYFP (SEQ ID NO: 2 encoded by SEQ ID NO: l) and phiYFP mutants Y1 (SEQ ID NO:4 encoded by SEQ ID NO:3), M0 (SEQ ID NO:6 encoded by SEQ ID NO:5), M1 (SEQ ID NO: 8 encoded by SEQ ID NO:7), M1 humanized (ID NO: 10 encoded by SEQ ID NO:9,), M1G1 (encoding SEQ ID NO:18 encoded by SEQ ID NO:17), and M1C1 (SEQ ID NO:20 encoded by SEQ ID NO:19). None of these nucleic acid molecules disclosed in the specification exhibit lower than 96% identity to the full length of phiYFP (SEQ ID NO: 2 encoded by SEQ ID NO: l). It is worth noting that the phiYFP shares only about 50% identity with well characterized GFP (from jelly fish), and there is no evidence on the record supporting that the amino acid residue required for exhibiting green fluorescence for GFP can be directly applied to the aligned corresponding amino acid residues present in phiYFP. Therefore, it would require undue experimentation for an artisan to determine which amino acids are necessary and sufficient for phiYFP-M1 (i.e. the claimed SEQ ID No. 10) to be a yellow fluorescent protein to support the breadth of the claims.

In the art, it is unpredictable how variations of sequences in a given fluorescent protein would affect its function as a fluorescent protein. For instance, **Shagi et al.** teaches that homologs of the green fluorescent protein (GFP), including the recently described GFP-like domains of certain extracellular matrix proteins in Bilaterian organisms, are remarkably similar at the protein structure level, yet they often perform totally unrelated functions, thereby warranting recognition as a superfamily (See Shagin et al., GFP-like proteins as ubiquitous metazoan superfamily: evolution of functional features and structural complexity, *Mol Biol Evol.*

21(5):841-50, 2004). Additionally, **Sample et al.** teaches that FP family members generate their chromophores autocatalytically through a series of posttranslational modifications. The fluorescence characteristics of GFP-family members are influenced in important ways by the *local microenvironment surrounding the chromophore* (See abstract, Sample et al. et al., The structure and function of fluorescent proteins, *Chem Soc Rev.* 38(10):2852-64, 2009). Furthermore, **Parmley et al.**, 2007 teaches that even silent SNPs (single nucleotide polymorphisms) encoding the same amino acid residues are not necessarily neutral with regard to their effects on the functions of polypeptides, and there are two additional mechanisms affecting the function of a given polypeptide: (1) modification of protein structure and activity, mediated by induction of translational pausing during co-translational protein folding, and (2) modification of protein abundance mediated by alteration in mRNA stability via changed secondary structures of mRNA, which in turn leads to perturbation in protein synthesis (See abstract, Parmley et al., How do synonymous mutations affect fitness? *Bioessays*, 29(6): 515-9, 2007). In other words, alterations in either protein folding or translational efficiency could result in changed protein functions encoded by synonymous mutations.

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention as recited in claims 1, 5-8, 13, 17, 28, and 30-33.

Applicant's arguments

Applicant argues that the art teaches which amino acids encode the structure that provided for fluorescence and thus should be conserved, and, conversely, which amino acid residues could be modified without losing fluorescence; see, e.g., Yang et al. ((1996) Nat.

Biotech 14:1246-51); Ormo et al. ((1996) Science 273:1392-95); Matz et al. ((1999) Nat Biotech 17:969-973); Heim et al. ((1996) Current Biol. 6:178-182); Siemering et al. ((1996) Current Biol. 6(12):1653-63); Yang et al. ((1998)J Biol Chem 273(14):8212-8216); Wiedenmann et al. ((2000) PNAS 97(26):14091- 6); Bevis et al. ((2002) Nat. Biotechnol 20(1):83-7); Campbell et al. ((2002) PNAS 99(12):7877- 82); and Shaner et al. ((2004) Nat Biotechnol 22(12):1567-72), all of the record and discussed in greater detail in previous responses. Thus, the artisan would be enabled to predict exactly which amino acids of SEQ ID NO: 10 are conserved and should not be mutated versus those which are not conserved and could be mutated so as to retain fluorescence activity. Additionally, the specification teaches methods of testing these predictions, by teaching methods of making mutant nucleic acids encoding mutant proteins (p. 8, I. 21-p. 9, I. 9; see also p. 26, I. 8-11), and of testing these mutant nucleic acid, for example by transfecting the nucleic acids into cells in culture, waiting 20 hours, and imaging the cells on a fluorescence microscope (p. 29, I. 7-16). Thus, one of ordinary skill in the art would know how to isolate or design a multitude of other nucleic acid sequences that would encode fluorescent proteins encompassed by the pending claims (See pages 14-15 of Applicant's remarks filed on 04/07/2010).

Response to Applicant's arguments

As stated in the scope of enablement rejection documented in this office action, it is worth noting that the phiYFP shares only about 50% identity with well characterized GFP (from jelly fish), and there is no evidence on the record supporting that the amino acid residue required for exhibiting green fluorescence for GFP can be directly applied to the aligned corresponding amino acid residues present in phiYFP. Therefore, it would require undue experimentation for an artisan to determine which amino acids are necessary and sufficient for phiYFP-M1 (i.e. the claimed SEQ ID No. 10) to be a yellow fluorescent protein to support the breadth of the claims. In the art, **Sample et al.** teaches that FP family members generate their chromophores autocatalytically through a series of posttranslational modifications. The fluorescence characteristics of GFP-family members are influenced in important ways by the local microenvironment surrounding the chromophore (See abstract, Sample et al. et al., The structure and function of fluorescent proteins, *Chem Soc Rev.* 38(10):2852-64, 2009).

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Previous rejection of claims 1, 5-8, 13, 17, 28, and 30-33 under 35 U.S.C. 102(e) as being anticipated by Baubet et al. (Baubet et al., US 2008/0213879, publication date 09/04/2008, Division of US 6,936,475, which is a Continuation of PCT/EP01/07057, WO 2001/092300, filed on 06/01/2001), is ***withdrawn*** because the claims have been amended.

Amended claim 1 filed on 04/07/2010 reads as follows: An isolated nucleic acid molecule encoding a fluorescent protein, wherein said protein has at least 90% identity with full length SEQ ID NO: 10.

Amended claim 13 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to claim 1, wherein said nucleic acid comprises a sequence that is identical to a nucleotide sequence of at least 300 contiguous nucleotides in length of SEQ ID NO:9

Amended claim 28 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to the claim 1 which encodes full length SEQ ID NO: 10.

Amended claim 30 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to claim 1, having a nucleotide sequence comprising full length SEQ ID NO: 9.

Amended claim 31 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to Claim 1, wherein said nucleic acid molecule encodes a fluorescent protein having at least 95% identity with full length SEQ ID NO: 10.

Amended claim 32 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to claim 1, having a nucleotide sequence having at least 95% identity with full length SEQ ID NO:9.

Baubet et al. does not teach the limitation "wherein said protein has at least 90% identity with full length SEQ ID NO: 10" recited in claim 1. Claims 5-8, 13, 17, 28, and 30-33 depend from claim 1.

7. Previous rejection of claims 1, 5-8, 13, 17, 28, and 30-33 rejected under 35 U.S.C. 102(b) as being anticipated by Baubet et al. (PCT/EP01/07057, WO 2001/092300, filed on 06/01/2001 is ***withdrawn*** because the claims have been amended.

Amended claim 1 filed on 04/07/2010 reads as follows: An isolated nucleic acid molecule encoding a fluorescent protein, wherein said protein has at least 90% identity with full length SEQ ID NO: 10.

Amended claim 13 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to claim 1, wherein said nucleic acid comprises a sequence that is identical to a nucleotide sequence of at least 300 contiguous nucleotides in length of SEQ ID NO:9

Amended claim 28 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to the claim 1 which encodes full length SEQ ID NO: 10.

Amended claim 30 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to claim 1, having a nucleotide sequence comprising full length SEQ ID NO: 9.

Amended claim 31 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to Claim 1, wherein said nucleic acid molecule encodes a fluorescent protein having at least 95% identity with full length SEQ ID NO: 10.

Amended claim 32 filed on 04/07/2010 reads as follows: The nucleic acid molecule according to claim 1, having a nucleotide sequence having at least 95% identity with full length SEQ ID NO:9.

Baubet et al. (2001) does not teach the limitation "wherein said protein has at least 90% identity with full length SEQ ID NO: 10" recited in claim 1. Claims 5-8, 13, 17, 28, and 30-33 depend from claim 1.

Conclusion

8. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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Art Unit 1632